Population-based post-licensure safety surveillance

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With thanks to Paddy Farrington, Open University for contributing some SCCS slides

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Aims of the lecture

• Assess the role of vaccine -pharmacovigilance and epidemiological studies in safety assessment.
• To cover how this is done in different settings
• To understand the main designs used
• To focus on the self controlled case series design

• Neal Halsey has already given an overview on causality assessment, safety in clinical trials epidemiological designs
Vaccine Safety Assessment components

Vaccine Trials
reactogenicity

Pharmacovigilance (passive/active):
hypothesis generation, RAPID

Licensure

Individual causality assessment

Epidemiological studies
(hypothesis testing)

Signal Strengthening/assessment

Priority?

Plausibility, other data/methods, experts, other risks, interval from vaccine,....
Vaccine Pharmacovigilance

“the science and activities relating to the detection, assessment, understanding, prevention and communication of adverse events following immunization” - Global Vaccine Safety Blueprint

  “Effective vaccine pharmacovigilance systems are established in all countries.”

- **Minimal Capacity**
  - A national dedicated capacity
  - Health-care workers and others encouraged to report AEFI
  - Reporting forms for case safety reports
  - A national database or system
  - Harmonized methods and tools for the monitoring and investigation of AEFI

- **Enhanced Capacity**
  - The ability to carry out active surveillance rather than relying solely on spontaneous reporting
  - The ability to carry out epidemiological studies to test hypotheses
Detection - in Spontaneous Reporting systems
Detecting signals in Spontaneous Reporting systems

• Case counts – assess frequencies, trends, spikes…
• Careful clinical review (severe events)
• Observed v Expected rates
  – Expected from external data source – can be done sequentially using sequential methods to reduce false positives (Max-SPRT).
  – Allow for under-reporting
• Data mining – disproportionality analysis*
  – e.g. 10% of all adverse events reported after MMR are convulsions compared to 5% of all adverse events after other vaccinations. Proportional reporting ratio = 2. Test with chi-square.

Active surveillance

- Large linked databases for active surveillance
  - Health Insurance (managed care organisation data)
    - USA – Vaccine Safety datalink, PRISM
    - Taiwan - National data for hospitalisations linked to vaccination data
  - General Practice data
    - UK – Clinical Practice Research Datalink (used for maternal pertussis)
- Hospital based active reporting
  - Canada – IMPACT system
    - Covers 80% of all paediatric admissions
    - Special nurses scrutinise all admissions for possible adverse events (and vaccine preventable diseases)
    - Causality assessment largely based on biological plausibility
- Active follow up of a cohort
Methods for detection in large linked databases

• Start with a list of events of interest (e.g. 30 events)
• Compare cumulative reports to a comparison group
  – Historical incidence
  – Concurrent cohort (unvaccinated)
  – Self controlled design (see later)
• Use Sequential monitoring (sequential probability ratio tests) – Rapid Cycle Analysis
Statistical test for sequential monitoring: log-likelihood ratio and relative risk following 2009 H1N1 inactivated vaccine of Bell’s palsy for adults ≥25 years.
Passive v Active

Passive
- Rapid
- Whole population (so rare events)
- Reports from many sources
- Under-reporting
- Subject to biases
- No unvaccinated comparator

Active
- Delays
- May not be whole population
- Restricted to events in database used
- Much less bias
- Unvaccinated comparator
- May “use up” the data you want for an epi study
Many other sources of safety signals

- Case-reports (literature, medical specialists, media, internet…)
- Clinical trials
- Biological mechanism
- Ecological studies
- Reports from other countries
Signal assessment

- Most signals will not need a full epidemiological study
- **Interim assessment (signal strengthening)**
  - Similar data in other countries, other data sources / analysis methods, plausibility, other causes (individual causality), expert review
- **Prioritisation and refinement**
  - Severe, new, large numbers given vaccine, size of risk, vaccine still in use, public/media/political interest, affect on coverage, alternatives…
  - What exactly is the hypothesis to be tested in a formal study…
Examples

• Hypersensitivity reactions in a national MMR campaign in Brazil – 2004 (Frietas et al vaccine 2013)
  – Detected in passive surveillance
  – Interim assessment
  – Rates compared between manufacturers
  – Manufacturer “A” rate 15.3 per 100,000 doses vs 1.2 and 0.6 for other manufactures
  – Recall of Brand A

• Deaths following PCV7 and Hib Vaccines in Japan 2011
  – Vaccines withdrawn
  – Rates compared to other countries (similar) and expert review of the 7 deaths with no clear causality.
  – Vaccine re-instated after 4 weeks
Epidemiological assessment
Main epidemiological designs for safety

- **Cohort**
  - Prospective parallel group, historical

- **Case-control**
  - Usually matched by the date of the event in the case.

- **Case only**
  - Self controlled case-series (SCCS) - MORE DETIALS TO FOLLOW…
  - Case cross-over

- **Case-coverage** (case-cohort) — see extra slides for UK study of Pandemrix and narcolepsy – odds of vaccination in cases from all of England compared to the odds of vaccination in the population (matched by time period and risk factors) using data from about 100 general practices across England.
Which design to use?

• The design will depend on the precise question and the data sources available.
• As with all epi-studies it is important to have a precise question (as is possible), case-definition (strict/less strict), exposure risk (and interval post vaccination), population of interest and likely important confounding variables.
• Data sources.....
  – Immunisation registries
  – Disease registers
  – Hospital Episode databases
  – Individual Hospital data
  – General Practice databases
  – Health Maintenance data bases
  – Prospective cohorts (e.g. whole birth cohorts followed up)

The “ideal” design vs strengths/limitations of data sources and best design for data available.
The origins of the SCCS method

• Solving a practical problem by Prof Paddy Farrington
SCCS: Why was the method developed?

- UK 1992: the MMR vaccine has been in use for 5 years.
- Cases of viral meningitis are reported soon after receipt of MMR vaccines containing the Urabe mumps strain.
- Discharge data from the administrative databases of 5 hospitals are searched.
- 32 cases of viral meningitis in children aged 12 – 24 months are identified.
- 13 of these had onsets 15 – 35 days after an MMR vaccine.

Is there an association between MMR vaccine and aseptic meningitis?
What was to be done?

- The catchment areas of the 5 hospitals were ill-defined.
- So a retrospective cohort study did not appear to be possible,
- … and the selection of controls from the cohort was prone to bias.
- A case-control study would have been difficult to undertake.
- And in any case results were needed rapidly.

Could a valid epidemiological study be based only on cases, that is, on children with viral meningitis?
What happened

- The case-series method was developed at PHE (HPA / PHLS) by Paddy Farrington and an increased risk shown.
- Urabe-containing MMR vaccines were withdrawn.
- A confirmatory record-linkage SCCS study was undertaken.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>$R_I$ in 15-35 day period after MMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile Convulsion or Aseptic Meningitis</td>
<td>1062</td>
<td>1.51 (1.21, 1.90)</td>
</tr>
<tr>
<td>Aseptic Meningitis</td>
<td>7</td>
<td>38.1 (4.3, 336)</td>
</tr>
</tbody>
</table>

Farrington et al (1995), Lancet
SCCS - How does it work?
(pictures to follow!)

- Fix an observation period, over which events are ascertained; the individuals with events are the cases.
- For each case obtain all exposures within that period.
- Subdivide the observation periods into exposure and age groups (and other time varying confounders).
- As in a cohort study, these are treated as fixed. Unlike most cohort studies, exposures may be post-event.
- For each case, regard the interval in which the event occurs as random.
Observation period

(V = time of vaccine doses if given)

Risk period 1

Risk period 2

Control periods

Age group boundaries
**Time line for one case (id 9) given one vaccine**

![Time line diagram]

**Data for child 9**

<table>
<thead>
<tr>
<th>Indiv</th>
<th>Interval</th>
<th>Length</th>
<th>Age_grp</th>
<th>Exp_grp</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>1</td>
<td>77</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>21</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>14</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>60</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>133</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>50</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Statistical analysis in STATA

The statistical model is **product multinomial**, which can be fitted by conditional **Poisson regression**.

![Diagram](image)

- **Fits conditional Poisson model**
- **Number of events**
  - `xtpoisson events i.exp_grp i.age_grp, fe i(indiv) offset(loglength) irr`
  - Adjust for interval lengths
  - Stratify by individual (conditional)
  - Quote results as relative risks
  - Exposure and age groups (i. tells stata we have factors)
What is the case series method?

• It is a conditional cohort method: exposures are regarded as fixed, event times as random.

• Follow-up is not censored at event.

• The method can be used with independent recurrent events, or uncommon non-recurrent events.

• Only cases are required: estimation is within-individuals.

• Cases must clearly be an unbiased set of cases (not any collection of cases!)

• The analysis is self-matched, thus eliminating the effect of fixed confounders.

• It has been programmed in standard statistics packages.
Main advantages

- **Only cases** are required, hence data are relatively easy and cheap to assemble.
- **All fixed confounders** are controlled.
- **Temporal variation** in the event rate is explicitly modelled as in a cohort study.
- **Independent recurrences** can be handled in the same framework.
- **Exposures** need not be transient.
- **Power** is often good.
Main limitations

- Only estimates of relative risk are available - absolute risks are not estimated.
- Occurrence of an event should not appreciably increase mortality.*
- Occurrence of an event should not affect subsequent exposure history.*

* Recent developments extend applicability of the method to situations where these last conditions are not met, but at the cost of greater methodological complexity.
Using only cases:

Relative incidence of convulsions in 2\textsuperscript{nd} week after measles vaccine

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Study (Ref.)</th>
<th>Relative Incidence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA study</td>
<td>Barlow \textit{et al} 2001</td>
<td>2.83</td>
<td>(1.44, 5.55)</td>
</tr>
<tr>
<td>UK study</td>
<td>Farrington \textit{et al} 1995</td>
<td>3.04</td>
<td>(2.27, 4.07)</td>
</tr>
</tbody>
</table>

Cohort study, 679,942 kids
Case series, 952 cases
Controlling confounding:

Asthma exacerbation and flu vaccine


Cohort and case series studies in asthmatic children aged 1 – 6 years in 1995/6. Risk period: 2 weeks after flu vaccine.

<table>
<thead>
<tr>
<th>Method</th>
<th>Sample size</th>
<th>RI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort, unadjusted</td>
<td>70 753</td>
<td>3.29</td>
<td>(2.55, 4.15)</td>
</tr>
<tr>
<td>Cohort, adjusted</td>
<td>70 753</td>
<td>1.39</td>
<td>(1.08, 1.77)</td>
</tr>
<tr>
<td>Case series</td>
<td>2075 cases</td>
<td>0.98</td>
<td>(0.76, 1.27)</td>
</tr>
</tbody>
</table>

The cohort results are subject to indication bias. The case series results are unaffected by this bias.
Example: GBS, flu vaccine and flu-like illness

Data source: General Practice Research Database (GPRD)
Observation period: all time within GPRD in 1990 – 2005
Two types of exposures: flu vaccination and flu-like illness.
Risk periods: 0-30, 31-60, 61-90 days after vaccine/onset
Pre-exposure risk period: 2 weeks
Age groups: 12 periods over 0 – 115 years
Seasonal groups: calendar month
Repeat episodes: included if > 6 months separation
Results

775 distinct episodes in 690 individuals

Flu vaccine:
0 – 30 days: RI = 0.58 (0.18, 1.86)
0 – 90 days: RI = 0.76 (0.41, 1.40)

Influenza-like illness:
0 – 30 days: RI = 16.64 (9.37, 29.54)
0 – 90 days: RI = 7.35 (4.36, 12.38)
Interval between influenza-like illness and GBS

## Exposures and outcomes investigated using SCCS

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>TB</td>
</tr>
<tr>
<td>Infections</td>
<td>Hip fracture</td>
</tr>
<tr>
<td>Flying</td>
<td>Stroke</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Death</td>
</tr>
<tr>
<td>Statins</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Invasive dental treatment</td>
<td>Bells Palsy</td>
</tr>
<tr>
<td>Foot ulceration</td>
<td>DVT</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Gait disturbance</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>Bacterial infection</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Asthma</td>
</tr>
<tr>
<td>Many vaccines</td>
<td>Convulsions, GBS, Autism, ITP,</td>
</tr>
<tr>
<td></td>
<td>Aseptic Meningitis, Intussusception</td>
</tr>
</tbody>
</table>

All need careful consideration of the assumptions of SCCS
Alternative case – only design – the case-cross over
Case Cross-over study: For people with MS, are relapses associated with vaccines? (slide thanks to Neal Halsey)

### Table 3. Risk of Relapse Associated with Exposure to Specific Vaccines in the Two Months Preceding a Relapse in 643 Patients with Multiple Sclerosis.*

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Percent Exposed</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk Period</td>
<td>Control Periods</td>
</tr>
<tr>
<td>Any vaccine</td>
<td>2.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Tetanus alone</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Combined tetanus</td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Influenza</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Monovalent vaccines</td>
<td>2.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Combined vaccines</td>
<td>0.3</td>
<td>1.1</td>
</tr>
</tbody>
</table>

*For each patient there was one risk period and four control periods.

Analysis is conditional logistic regression.
Consistency across studies

- The best designs may vary – but key to causality is consistency from well designed studies.
Same question – different designs
Pandemic flu vaccine (Pandemrix) and narcolepsy

- 6 countries have looked at Pandemrix (Cohort, case-coverage, case-control)
- Canada at Arepanrix (Cohort, SCCS, Test – negative)
### Association between Pandemrix and narcolepsy: study results

<table>
<thead>
<tr>
<th>Country</th>
<th>Study design</th>
<th>Definition of onset</th>
<th>Risk RR/OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>Cohort</td>
<td>1st contact to HC</td>
<td>12.7</td>
<td>6.1 – 30.8</td>
</tr>
<tr>
<td>France</td>
<td>Case-control</td>
<td>Date for referral to MSLT</td>
<td>5.1</td>
<td>2.11 – 2.3</td>
</tr>
<tr>
<td>Ireland</td>
<td>Cohort</td>
<td>1st contact to HC</td>
<td>13.0</td>
<td>4.6 – 34.7</td>
</tr>
<tr>
<td>Norway</td>
<td>Cohort</td>
<td>Date of EDS recorded by patient/family</td>
<td>14.5*</td>
<td>Not reported</td>
</tr>
<tr>
<td>Sweden</td>
<td>Ecologic Cohort</td>
<td>Date of diagnosis G47.4</td>
<td>4.06</td>
<td>2.87 – 5.58</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Case-Coverage</td>
<td>Date of EDS recorded by GP</td>
<td>14.4</td>
<td>4.3-48.5</td>
</tr>
</tbody>
</table>

*Reported as at least 10-fold increase in final scientific publication
Same question – similar designs
Rotavirus vaccine and Intussusception

- Almost all studies have used SCCS across US, Australia, Mexico, Brazil, UK, Singapore… All with similar results showing a risk after dose 1 and a lower risk after subsequent doses.
- Needed to allow for the fact that intussusception event is a contra-indication.

**Relative incidence of IS 1-21 days post monovalent RV dose 1 by study**
Summary

- Pharmacovigilance and individual causality assessments help identify signals and rapidly evaluate them.
- Population based epidemiological studies are important to help assess causality.
- Optimal design depends on question and data sources.
- Large linked data bases are the future BUT how do we use them best – detection vs testing!
EXTRA SLIDES: Useful resources

- ADVANCE consortium looking at vaccine benefit risk http://www.advance-vaccines.eu/
- SCCS Website: http://statistics.open.ac.uk/sccs
  Created by Heather Whitaker – to be updated in the next year or so…
- Useful overview of case-only methods: Farrington, Vaccine 2005, 2064-70. Control without separate controls:…
Comparing designs

The exposure and event history for four individuals

- **id1**: Blue line is 200 days person follow-up time, star is vaccination time and triangle event time.

**Cohort**
- Rate of events in 30 day post vaccination risk period (red) compared to non-risk period (blue), follow-up stops at an event (if non-recurring). Poisson regression or survival analysis can be used.

**Matched case-control**
- Cases are matched to non-cases (for example id 1 to 3 and id 2 to 4) and the odds of vaccination in the 30 days prior to the case event time (orange) compared using conditional logistic regression.

**Case-crossover**
- Just using cases (id 1 & 2) the odds of vaccination in 30 days prior to the event time (orange) is compared to the previous 30 day period (green) using conditional logistic regression.

**SCCS**
- Just using cases (id 1 & 2) event rate 30 days post vaccination (red) compared to non-risk period (blue) using conditional Poisson regression.
Pandemrix H1n1 2009 vaccine and narcolepsy in England (Miller et al, Lancet, 2013)

- Vaccination history from GPs
- Design
  - Case-coverage design comparing proportion of cases vaccinated to age, period matched population data from 100 GP practices.
  - Analysis by logistic regression with an “offset” in the model for the log-odds of the matched population coverage.
Cases by onset date and vaccination status

The graph shows the number of narcolepsy cases by year and month, differentiated by vaccination status (vaccinated before symptoms, unvaccinated, Pandemrix vaccination uptake). The percentage of population vaccinated in the month is also indicated on the right side of the graph.
Coverage data for pandemic vaccine from primary care databases in England

Non risk group

Risk group
Results

• Case Coverage
  – Of 17 cases in the post vaccine period 10 were vaccinated (matched coverage about 16%)
  – OR 14.4, 95% CI (4.3-48.5)